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Factors associated with *Staphylococcus aureus* nasal carriage among healthy people in Northern China

X. Yan^{1,5}, Y. Song², X. Yu³, X. Tao^{1,5}, J. Yan³, F. Luo², H. Zhang^{1,5}, J. Zhang³, Q. Li², L. He^{1,5}, S. Li², F. Meng^{1,5}, J. Zhang^{1,5} and H. Grundmann⁴

1) State Key Laboratory for Infectious Disease Prevention and Control, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, 2) Chaoyang Center for Disease Control and Prevention, Beijing, China, 3) Heilongjiang provincial Centre for Disease Control and Prevention, Harbin, China, 4) Department of Medical Microbiology, University Medical Center Groningen, Rijksuniversiteit Groningen, The Netherlands and 5) Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China

Abstract

There is still limited knowledge about the prevalence and risk factors of nasal carriage for *Staphylococcus aureus* among healthy carriers in China. We investigated 2448 healthy adults (≥ 18 years of age) from Beijing ($n = 1530$) and Harbin ($n = 918$) by nasal screening. Participants were checked for carriage of *S. aureus*, and health-related and demographic information between 2009 and 2011 was gathered. A total of 403 *S. aureus* (403/2448, 16.5%) were recovered, 8 of which were methicillin resistant (8/2448, 0.33%). Three factors were independently associated with *S. aureus* nasal carriage: Harbin as city of residence (odds ratio (OR) = 2.0, 95% confidence interval (CI) = 1.41 to 2.85), age ≤ 24 years (OR = 1.77, 95% CI = 1.30–2.44) and non-Han ethnicity (OR = 1.58, 95% CI = 1.05 to 2.38). On the basis of population genetic analysis using multiple locus variable number of tandem repeats analysis (MLVA) and *spa* typing, MLVA complex (MC) 398 and MC5a were the most prevalent clonal lineages in this collection. In multivariate models, residing in Harbin (OR = 1.77, 95% CI = 1.07–2.92) and having household members in the healthcare profession (OR = 3.69, 95% CI = 1.14–11.92) were factors associated with carriage of clonal lineage MC398. On the other hand, female sex (OR = 3.15, 95% CI = 1.35–7.33) and a history of chronic liver disease (OR = 16.93, 95% CI = 2.91–98.59) were associated with the clonal lineage MC5a. The three most common *spa* types were t571 (10.9%), t189 (9.9%) and t701 (7.2%). These findings provide insight into the determinants of nasal carriage and ecology for some of the most successful strains of *S. aureus* among healthy people in Northern China.

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The first three authors contributed equally to this article, and all should be considered first author.

Corresponding author: H. Grundmann, Department of Medical Microbiology, University Medical Center Groningen, Rijksuniversiteit Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

Corresponding author: J. Zhang, State Key Laboratory for Infectious Disease Prevention and Control, Chinese Center for Disease Control and Prevention, 155 Changbai Road, Changping District, Beijing 102206, China

E-mails: zhangjianzhong@icdc.cn (J. Zhang), h.grundmann@umcg.nl (H. Grundmann)

Introduction

Staphylococcus aureus is a leading cause of hospital-associated and community-onset bacterial infections in humans. The most important factors which contribute to the success of *S. aureus* as a pathogen are believed to be the ability to persist as a commensal, resistance to multiple antimicrobial agents and the diverse repertoire of virulence determinants [1,2].

Staphylococcus aureus can colonize multiple sites of the human body, but the anterior nares appear to be the main

ecological niche [3]. In healthy whites, it is estimated that 20% are persistent carriers and an additional 30% intermittent carriers, while approximately 50% are noncarriers. There are three lines of evidence that support the view that *S. aureus* nasal carriage is associated with a higher chance to develop staphylococcal infections. First, the rates of infection are higher in persistent carriers than others [4]. Second, high-resolution molecular typing using pulsed-field gel electrophoresis has shown that infecting strains of *S. aureus* were indistinguishable from carriage isolates previously isolated from the external nares of patients who later developed an invasive infection [5,6]. Finally, eradication of this microorganism is regarded as an effective means for reducing infections in surgical and dialysis patients [4,7].

Over the past decade, reports about community-onset methicillin-resistant *S. aureus* (MRSA) infections have raised concern about the public health implications of *S. aureus* transmission among healthy individuals. Therefore, unravelling the risk factors for carriage of *S. aureus* is crucial for understanding the transmission potential of both MRSA and methicillin-sensitive *S. aureus* (MSSA). To date, there have been only few reports on the prevalence and the risk factors of *S. aureus* nasal carriage in China. Previous studies revealed 15.4% to 23.1% *S. aureus* nasal carriage in Chinese medical students from different regions, of which 3.0% to 9.4% were MRSA [8,9]. Another study revealed a similar nasal carriage rate (20%) in 1044 military volunteers from Beijing with no MRSA strains identified [10]. Both studies focused on populations that typically lived under crowded conditions and thus had higher opportunities for transmission. It still remains unclear whether carriage rates and risk factors among the Chinese general population are in the same range. We therefore performed a population-based survey to determine the prevalence and risk factors of *S. aureus* nasal carriage in two cities in Northern China.

Materials and methods

Population and study design

A cross-sectional study was conducted in two northern cities, Beijing and Harbin. Individuals presenting for mandatory occupational health screenings from food and public service industries as well as public health workers were chosen as healthy volunteers for the present survey. Between 2009 and 2011, 1530 and 918 nasal swabs were sampled in Beijing and Harbin, respectively. A self-administered questionnaire was completed by each volunteer to collect pertinent demographic and medical information, as well as factors that are potentially related to *S. aureus* nasal carriage and transmission as identified in the literature.

Bacterial strains

Nasal swabs from both nares were enriched in tryptic soy broth (Oxoid, Basingstoke, England, UK) with 7% NaCl at 37°C for 24 hours, plated onto mannitol salt agar (Oxoid) and cultured at 37°C for 24 hours. Presumptive *S. aureus* colonies were confirmed by colony morphology, Gram staining, catalase production, coagulase production using the Slidex Staph Plus kit (Murex Biotech, Kent, France) and polymerase chain reaction (PCR) for the *nuc* and *mecA* genes [11].

Molecular typing and Panton-Valentine leukocidin (*pvl*) gene detection

Multiple locus variable number of tandem repeats analysis (MLVA) was carried out for all 403 isolates, and representative strains of each MLVA complex (MC) were analysed by multi-locus sequence typing (MLST) in a previous unpublished study. All the isolates were also characterized using *spa* typing [12]. The *pvl* gene was detected by PCR, as previously described [13].

Simpson's index of diversity and 95% confidence intervals were used to calculate the genetic diversity of strains by Ridom EpiCompare software, version 1.0 (Ridom GmbH, Münster, Germany).

Potential risk factors

Several variables were investigated as potential risk factors of *S. aureus* nasal carriage. These included general demographic variables such as age, sex, ethnicity and immune system impairment. Immune system impairment was defined as diagnosis of primary and secondary immunodeficiency disorders, and systemic immune suppressive therapy was also included. Additional risk factors, such as skin and soft tissue infections, hospitalization, use of antibiotics and frequent contact with animals or animal products in the past 6 months, were also recorded. At the same time, we were also interested in transmission between family members at the household level. Therefore, risk factors of other household members were also investigated (Online Appendix S1).

Statistical analysis

The questionnaires were manually imported into EpiData (v3.02) software (EpiData Association, Odense, Denmark). Statistical comparisons were performed with SPSS (PASW Statistics 18.0.3) software (IBM, Armonk, NY). The only continuous variable, age, was transformed into a categorical variable using the quartiles of the frequency distribution (≤ 24 , $>24-30$, $>30-40$, >40 years). Furthermore, the different occupations were grouped into four categories that involved the following: (1) physical contact with healthy people (such as hairdressing and kindergarten teacher); (2) physical contact with animals or animal products (such as animal handlers, meat

processing personnel, cooks); (3) physical contact with patients and patient material (such as healthcare personnel); and (4) nonphysical contact with people or animals (remaining occupations). Categorical variables were compared by the chi-square test or by the Fisher exact test. Odds ratios (OR), 95% confidence intervals (CI), and *p* values were calculated. A *p* value of ≤ 0.05 was considered statistically significant. Logistic regression models were applied to determine independent risk factors. Multiple logistic regression analysis was carried out by entering all the independent variables associated with the outcome, with an α error accepted to the level of $p < 0.2$.

Ethical considerations

The study was approved by the ethical committee of the National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention. Written consent was obtained from all participants.

Results

Characteristics of study subjects

From 2009 to 2011, a total of 2448 volunteers from two cities were enrolled onto this study, 1530 of whom were from Beijing and 918 from Harbin. The majority of the volunteers were women (1617/2446, 66.1%). Ages ranged from 18 to 74 years (mean 32.4, standard deviation 10.3). Of the 2448 volunteers,

403 (16.5%) carried *S. aureus*, including 8 MRSA carriers (0.33%). *Staphylococcus aureus* carriage in Harbin (197/918, 21.46%) was more frequent than in Beijing (206/1530, 13.46%) ($p < 0.001$).

Epidemiological factors associated with *S. aureus* carriage

Variables associated with *S. aureus* carriage in the univariate analysis are shown in Table 1. Statistically significant factors included: age ≤ 24 years, ethnicity, non-Han, residing in Harbin, immune system impairment and hospitalization of a household member within the past year. Three independent risk factors remained associated in the multiple logistic regression analysis (Table 1). These consisted of Harbin as city of residence (OR = 2.0, 95% CI = 1.41 to 2.85), age ≤ 24 years (OR = 1.77, 95% CI = 1.30–2.44) and non-Han ethnicity (OR = 1.58, 95% CI = 1.05 to 2.38).

Factors associated with strains belonging to successful clonal lineages

In the present collection MC398 and MC5a were the most prevalent complexes, representing 21.0% and 11.7% of all isolates, respectively. The present study sought to assess the factors associated with nasal carriage for strains belonging to these two lineages. Multivariate logistic regression showed that residing in Harbin (OR = 1.77, 95% CI = 1.07–2.92) and having household members in the healthcare profession (OR = 3.69,

TABLE 1. Univariate and multivariate analysis of risk factors associated with *Staphylococcus aureus* nasal carriage in 2446 healthy people in Northern China during 2009–2011

Characteristic	Carriers (n = 400), n (%)	Noncarriers (n = 2046), n (%)	Univariate			Multivariate logistic		
			OR	95% CI	p	OR	95% CI	p
Sex, female (n = 1617)	249 (15.4%)	1368 (84.6%)	0.82	0.65–1.02	0.073			
Age								
≤ 24 years (n = 661)	135 (20.4%)	526 (79.6%)	1.52	1.13–2.06	0.001	1.77	1.30–2.44	<0.001
>24 to 30 years (n = 642)	101 (15.7%)	541 (84.3%)	1.11	0.81–1.52	0.526	1.30	0.94–1.80	0.116
>30 to 40 years (n = 584)	84 (14.4%)	500 (85.6%)	1.00	0.72–1.39	0.988	1.01	0.72–1.43	0.939
Race, non-Han (n = 147)	34 (23.1%)	113 (76.9%)	1.59	1.07–2.37	0.03	1.58	1.05–2.38	0.027
City of residence								
Beijing (n = 1229)	171 (13.9%)	1058 (86.1%)	1.03	0.74–1.44	0.84	1.16	0.85–1.64	0.390
Harbin (n = 820)	175 (21.3%)	645 (78.7%)	1.74	1.24–2.42	0.00	2.00	1.41–2.85	<0.001
Occupation								
Contact with animal products (n = 775)	139 (17.9%)	636 (82.1%)	1.75	0.73–4.17	0.21			
Contact with patients (n = 66)	10 (15.2%)	56 (84.8%)	1.43	0.48–4.22	0.519			
Nonphysical contact with healthy people (n = 1531)	240 (15.7%)	1291 (84.3%)	1.49	0.63–3.51	0.366			
Education								
Primary school (n = 125)	16 (12.8%)	109 (87.2%)	0.34	0.08–1.46	0.148			
Middle school (n = 1107)	184 (16.6%)	923 (83.4%)	0.47	0.12–1.82	0.271			
High school (n = 791)	132 (16.7%)	659 (83.3%)	0.47	0.12–1.83	0.275			
University or higher (n = 407)	64 (15.7%)	343 (84.3%)	0.44	0.11–1.73	0.237			
Immunity system disease, yes (n = 6)	3 (50%)	3 (50%)	5.16	1.04–25.65	0.045			
Hospitalization in past half year, yes (n = 31)	7 (22.6%)	24 (77.4%)	1.51	0.65–3.53	0.343			
Antibiotic use in past half year, yes (n = 380)	66 (17.4%)	314 (82.6%)	1.09	0.82–1.46	0.561			
Frequent skin puncture in past half a year, yes (n = 126)	20 (15.9%)	106 (84.1%)	0.97	0.59–1.58	0.898			
Regular contact sports activities, yes (n = 229)	39 (17.0%)	190 (83.0%)	1.06	0.74–1.53	0.741			
Smoking								
Ex-smoker (n = 289)	41 (14.2%)	248 (85.8%)	0.83	0.58–1.18	0.295			
Smoker (n = 413)	67 (16.2%)	346 (83.8%)	0.97	0.73–1.30	0.835			
Regular contact with living animals, yes (n = 215)	32 (14.9%)	183 (85.1%)	0.89	0.60–1.31	0.548			
Household member hospitalization within 1 year, yes (n = 97)	23 (23.7%)	74 (76.3%)	1.63	1.01–2.64	0.045			

OR, odds ratio; CI, confidence interval.

TABLE 2. Univariate and multivariate analysis of risk factors associated with the MC398 strain in 391 *Staphylococcus aureus* carriers in Northern China during 2009–2011

Characteristic	MC398 carrier (n = 80)	Non-MC398 carrier (n = 311)	Univariate			Multivariate logistic		
			OR	95% CI	p	OR	95% CI	p
Inhabitant city								
Harbin (n = 168)	44 (26.2%)	124 (73.8%)	1.88	1.10–3.21	0.021	1.77	1.07–2.92	0.027
Other (n = 52)	9 (17.3%)	43 (82.7%)	1.11	0.48–2.54	0.807			
City of birth								
Harbin (n = 75)	22 (29.3%)	53 (70.7%)	3.53	1.12–11.13	0.032			
Other (n = 278)	54 (19.4%)	224 (80.6%)	2.05	0.70–6.02	0.192			
Skin and soft tissue infection in past half a year, yes (n = 6)	3 (50%)	3 (50%)	3.97	0.79–20.08	0.095			
Hospitalization in past half year, yes (n = 7)	3 (42.9%)	4 (57.1%)	2.97	0.65–13.55	0.160			
Regular contact sport activities, yes (n = 39)	12 (30.8%)	27 (69.2%)	1.84	0.89–3.81	0.103			
Household members who have a profession in healthcare, yes (n = 13)	6 (46.2%)	7 (53.8%)	3.49	1.14–10.68	0.029	3.69	1.14–11.92	0.029

OR, odds ratio; CI, confidence interval.

95% CI = 1.14–11.92) were factors associated with increased risk of carrying MC398 strains (Table 2). On the other hand, being of female sex (OR = 3.15, 95% CI = 1.35–7.33) and having a history of chronic liver disease (OR = 16.93, 95% CI = 2.91–98.59) heightened risk associated with MC5a carriage (Table 3).

Spa typing and Panton-Valentine leukocidin (pvl) gene detection

In total, the 403 isolates were assigned to 77 *spa* types, including 10 novel *spa* types, where 56 *spa* types were identified in Beijing and 42 in Harbin. Nineteen *spa* types were found in both cities, corresponding to 69.98% of all isolates. The top 11 *spa* types in both cities are shown in Table 4. The most commonly encountered *spa* types in this study were t571/CC398/ST398/MC398 (10.9%), t189/CC1/ST2139/MC437 (9.9%) and t701/ST6/ST2114/MC1933 (7.2%). Furthermore, our analyses revealed that carriage isolates had the same genetic diversity in both sampling locations, with a diversity index of 0.952 (0.941–0.964).

Moreover, the 8 MRSA strains belonged to different *spa* types. Two isolates had *spa* type t034/CC398/ST398/MC398, and one isolate each of *spa* type t2431/Singleton/ST2799/MC482, t437/CC59/ST59/MC621 and t116/CC45/MLST45/

MC45. The remaining two MRSA isolates were not typeable by *spa* typing.

Interestingly, the *pvl* gene was only detected among nine MSSA isolates (9/403, 2.2%), of which two had *spa* type t002/CC5/ST5/MC5a and one each had *spa* type t011/CC398/ST398/MC398, t091/CC7/ST7/MC7, t1376/CC88/ST2148/MC5b, t701/CC6/ST2114/MC1933, t167/CC5/ST25/MC674, t645/CC121/ST123/MC123 and t7611/CC22/ST22/MC22.

Discussion

We found nasal carriage with *S. aureus* in 16.5% of our study population. This finding coincides with the prevalence observed among recruits in a military camp (16%) [10] and medical college students in another study (15.4%) [9]. Cross-sectional studies conducted outside of China found prevalence estimates ranging from 8% to 37% among different populations, where 0% to 8.6% was MRSA [14–17]. The low prevalence of MRSA (0.36%) and the heterogeneity of *spa* types suggest that there were no singularly expanding MRSA clones among the study population.

Higher *S. aureus* carriage rates were published for whites [18,19], men [20], individuals with obesity [14], children [9] and

TABLE 3. Univariate and multivariate analysis of risk factors associated with the MC5a strain in 391 *Staphylococcus aureus* carriers in Northern China during 2009–2011

Characteristic	MC5a carrier (n = 42)	Non-MC5a carrier (n = 349)	Univariate			Multivariate logistic		
			OR	95% CI	p	OR	95% CI	p
Sex, female (n = 241)	33 (13.7%)	208 (86.3%)	2.49	1.15–5.35	0.020	3.15	1.35–7.33	0.008
Race, non-Han (n = 33)	6 (18.2%)	27 (81.8%)	1.99	0.77–5.14	0.156			
Chronic liver disease history, yes (n = 6)	3 (50.0%)	3 (50%)	8.85	1.73–45.34	0.009	16.93	2.91–98.59	0.002
Smoking								
Nonsmoker (n = 285)	33 (11.6%)	252 (88.4%)	2.71	0.80–9.11	0.108			
Ex-smoker (n = 40)	6 (15.0%)	34 (85.0%)	3.65	0.86–15.51	0.080			

OR, odds ratio; CI, confidence interval.

TABLE 4. Top 11 *spa* types of *Staphylococcus aureus* in two cities

<i>spa</i> type	<i>n</i>	%	MLVA complex (<i>n</i>)
Beijing			
t189	24	11.65%	MC437 (18), NM (6)
t701	20	9.71%	MC1933 (14), NM (6)
t002	18	8.74%	MC5a (17), NM (1)
t571	17	8.25%	MC398 (16), NM (1)
t796	10	4.85%	MC7 (9), NM (1)
t437	10	4.85%	MC621 (10)
t127	10	4.85%	MC1 (8), NM (2)
t034	9	4.37%	MC398 (8), MC1933 (1)
t091	8	3.88%	MC7 (8)
t163	5	2.43%	MC621 (5)
t803	4	1.94%	MC15 (2), NM (2)
Total	135	65.53%	
Harbin			
t571	27	13.71%	MC398 (27)
t189	16	8.12%	MC437 (12), NM (4)
t034	14	7.11%	MC398 (12), MC674 (1), NM (1)
t127	11	5.58%	MC1 (8), NM (3)
t002	9	4.57%	MC5a (9)
t701	9	4.57%	MC1933 (6), NM (2)
t078	8	4.06%	MC674 (7), NM (1)
t377	8	4.06%	MC8 (5), NM (3)
t796	7	3.55%	MC7 (5), NM (2)
t084	6	3.05%	MC15 (6)
t437	6	3.05%	MC621 (4), NM (2)
Total	121	61.42%	
Total			
t571	44	10.92%	
t189	40	9.93%	
t701	29	7.20%	
t002	27	6.70%	
t034	23	5.71%	
t127	21	5.21%	
t796	17	4.22%	
t437	16	3.97%	
t091	11	2.73%	
t078	10	2.48%	
t084	8	1.99%	
Total	246	61.04%	

MLVA, multiple locus variable number of tandem repeats analysis; MC, MLVA complex; NM, not belonging to any MC.

people with underlying diseases [4], especially skin disorders. We identified a significantly higher carriage among adults who are ethnically non-Han Chinese. Previous studies have shown that the human leukocyte antigen (HLA) DR3 antigen predisposes healthy individuals and transplant recipients to *S. aureus* nasal carriage with *S. aureus* [21,22]. Thus, population-specific frequencies of HLA haplotypes may explain differential susceptibilities between ethnic groups. However, HLA DR3 haplotype frequencies among the non-Han *S. aureus* carriers have not been investigated.

Interestingly, our study showed that the presence of household members who worked in the healthcare sector were more at risk for carrying strains belonging to the MC398 lineage. As previous studies have shown, there is high concordance between *S. aureus* strains isolated from medical staff and inpatients [23]. Additionally, it has been found that up to 65% of *S. aureus* carriers living within one household share genotypically identical strains [3]. These findings may indicate that healthcare personnel could contribute to the dissemination of MC398 strains between hospitals and the community—a topic that deserves more attention.

The bacterial population of *S. aureus* carriage isolates in our sample collection demonstrated the dominance of two clonal lineages against a background of a large genetic diversity. This diversity is consistent with previous findings among clinical MSSA strains [24]. Not surprisingly, there was a good correlation between *spa* types in healthy people of this study and the *S. aureus* strains isolated from hospital patients and outpatients with skin and soft tissue infections [25]. Five of the top seven *spa* types also represented the most frequent *spa* types among clinical isolates from patients with community-associated MSSA and hospital-associated MSSA infections [24]. This finding lends further support to the notion that *S. aureus* carriers are at risk of autoinfection.

In conclusion, our study showed that younger people (≤ 24 years) and ethnically non-Han individuals were more likely to be colonized by *S. aureus*. Furthermore, the presence of household members who are healthcare personnel appeared to be a risk factor for MC398 carriage. Importantly, approximately one third of all isolates showed the same *spa* types with community-associated MSSA and hospital-associated MSSA in some hospitals. These findings could be helpful for understanding the determinants of *S. aureus* nasal carriage and transmission routes of some successful strains in Northern China.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2014.08.023>.

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